

U.S. Application No. 09/517,224 filed March 2, 2000, now U.S. Patent No. 6,316,024; which is a division of U.S. Application No. 09/138,480 filed August 21, 1998, now U.S. Patent No. 6,056,973; which is a continuation-in-part of U.S. Application No. 08/949,046 filed October 10, 1997, now U.S. Patent No. 5,891,468; which claims the priority of U.S. Provisional Application No. 60/028,269, filed October 11, 1996, now abandoned, which are all incorporated herein by reference.--

In the Claims: Please cancel claims 1-28 and ~~add~~ new claims 29-59 as follows:

--29. ✓ A method of administering a therapeutic agent, comprising,  
administering via inhalation liposomes formed of vesicle-forming lipids and having a coating of hydrophilic polymer chains on the liposome outer surface, said liposomes having an entrapped therapeutic agent.

30. The method of claim 29, wherein the vesicle-forming lipid is selected from the group consisting of hydrogenated soy phosphatidylcholine, distearoylphosphatidylcholine sphingomyelin, diacyl glycerol, phosphatidyl ethanolamine, phosphatidylglycerol, distearyl phosphatidylcholine, and distearyl phosphatidylethanolamine.

31. The method of claim 29, wherein said liposomes further contain a shielded cationic lipid effective to impart a positive liposome-surface charge.

32. The method of claim 31, wherein the cationic lipid is selected from the group consisting of 1,2-dioleyloxy-3-

(trimethylamino) propane, N-[1-(2,3,-ditetradecyloxy)propyl]-N,N-dimethyl-N-hydroxyethylammonium bromide, N-[1-(2,3,-dioleyloxy)propyl]-N,N-dimethyl-N-hydroxy ethylammonium bromide, N-[1-(2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride; 3 $\beta$ [N-(N',N'-dimethylaminoethane) carbamoyl] cholesterol; and dimethyldioctadecylammonium.

33. The method of claim 31, wherein the cationic lipid is a neutral lipid derivatized with a cationic lipid.

34. The method of claim 29, wherein said hydrophilic polymer coating is composed of hydrophilic polymers selected from the group consisting of polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethyleneglycol, and polyaspartamide.

35. The method of claim 34, wherein said hydrophilic polymer coating is composed of polyethylene glycol chains having a molecular weight of between about 500 Daltons and about 10,000 Daltons.

36. The method of claim 29 wherein between about 1 mole percent and about 20 mole percent of the vesicle-forming lipids are derivatized with said hydrophilic polymer chains.

37. The method of claim 29, wherein at least a portion of the hydrophilic polymers are joined by a chemically releasable bond.

38. The method of claim 37, wherein said releasable bond is a disulfide bond.

39. The method of claim 37, wherein said releasable bond is a pH sensitive chemical linkage.

40. The method of claim 29, wherein the liposomes are composed of between about 70-90 mole percent hydrogenated soy phosphatidylcholine, about 1-20 mole percent distearylphosphatidylcholine derivatized with polyethyleneglycol and about 1-50 mole percent cholesterol.

41. The method of claim 29, wherein the liposome is about 0.1 to about 10 microns.

42. The method of claim 29, wherein the agent entrapped in the lipid vesicles is a polynucleotide capable of expressing a selected protein, when taken up by a target cell.

43. The method of claim 29, wherein the agent entrapped in the liposomes is an oligonucleotide or oligonucleotide analog effective for sequence-specific binding to cellular RNA or DNA.

44. The method of claim 29, wherein the agent entrapped in the liposomes is selected from the group consisting of DNA, proteins, and peptides.

45. The method of claim 29, wherein the agent entrapped in the liposomes is selected from the group consisting of antibiotics, antivirals, and antitumor drugs.

46. The method of claim 29, wherein said liposomes further contain a ligand attached to the distal end of at least a portion of said hydrophilic polymer chains.

47. The method of claim 29, wherein the liposomes further include a ligand attached the polar head group of at least a portion of the vesicle-forming lipids of the liposome.

48. The method of claim 46 or 47, wherein the ligand is an antibody or an antibody fragment.

49. The method of claim 48, wherein the ligand is a Fab' fragment of an antibody.

50. The method of claim 48, wherein the ligand is a single chain Fv antibody.

51. The method of claim 46 or 47, wherein the ligand specifically binds to an extracellular domain of a growth factor receptor.

52. The method of claim 51, wherein the receptor is selected from the group consisting of epidermal growth factor receptor, basic fibroblast growth factor receptor and vascular endothelial growth factor receptor.

53. The method of claim 46 or 47, wherein the ligand binds a receptor selected from the group consisting of E-selectin receptor, L-selectin receptor, P-selectin receptor, folate receptor, CD4 receptor,  $\alpha\beta$  integrin receptors and chemokine receptors.

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54. The method of claim 46 or 47, wherein the ligand is selected from the group consisting of folic acid, pyridoxal phosphate, sialyl Lewis<sup>x</sup>, transferrin, epidermal growth factor, basic fibroblast growth factor, vascular endothelial growth factor, VCAM-1, ICAM-1, PECAM-1, and RGD peptides.

55. The method of claim 46 or 47, wherein the ligand is selected from the group consisting of water soluble vitamins, apolipoproteins, insulin, galactose, Mac-1, PECAM-1/CD31, fibronectin, osteopontin, RGD sequences of matrix proteins, HIV GP 120/41 domain peptomers, GP120 C4 domain peptomers, T cell tropic isolates, SDF-1 chemokines, Macrophage tropic isolates, anti-cell surface receptor antibodies or fragments thereof, pyridoxyl ligands, RGD peptide mimetics, and anti-E-selectin Fab.

56. The method of claim 55, wherein the anti-cell surface receptor antibodies or fragments thereof is selected from the group consisting of anti-selectin and anti-VEGF pyridoxyl.

57. The method of claim 55, wherein the pyridoxyl ligand is selected from the group consisting of pyridoxal, pyridoxine, pyridoxamine, pyridoxal 5'-phosphate and N-(4'-pyridoxyl)amines.

58. The method of claim 29, wherein said liposomes are further comprised of a lipid derivatized by a diblock copolymer composed of a hydrophobic polymer chain covalently bound to the lipid and a hydrophilic polymer chain, the hydrophobic and hydrophilic chains being joined by a bond effective to release the hydrophilic polymer chains in response to an existing or an induced physiologic condition, thereby exposing the hydrophobic polymer chains.

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59. The method of claim 58, wherein said hydrophobic polymer is selected from the group consisting of polypropylene oxide, polyethylene, polypropylene, polycarbonate, polystyrene, polysulfone, polyphenylene oxide and polytetramethylene ether. --

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FOOTNOTES